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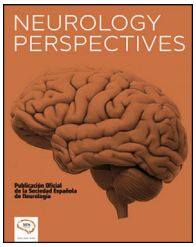

REVIEW

Multiple sclerosis and rheumatic diseases: Behçet disease, sarcoidosis, and Sjögren syndrome

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KEYWORDS
Behçet disease;
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Abstract
Introduction: Multiple sclerosis can be associated with a range of rheumatic processes. Behçet disease is a relapsing, multisystemic, immune-mediated chronic vasculitic disorder of unknown aetiology, whose symptoms overlap with those of many autoinflammatory processes. Sarcoidosis is a universally distributed multisystem granulomatous disease. Sjögren syndrome is a chronic, autoimmune, inflammatory disease characterised by lymphocytic infiltration in exocrine glands, which causes xerostomia (dry mouth) and xerophthalmia (dry eyes). The most frequent extraglandular manifestations of the syndrome are musculoskeletal problems.
Development: We describe the most significant neurological complications of these rheumatic diseases, as well as the pharmacological treatments that may be indicated for these conditions and the possible contraindications in patients receiving treatment for multiple sclerosis.
Conclusions: We provide a series of recommendations for the treatment of patients with multiple sclerosis who also present with Behçet disease, sarcoidosis, or Sjögren syndrome. Co-presence of any of these rheumatic diseases constitutes a contraindication for some treatments.
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PALABRAS CLAVE
Behcet;
Esclerosis múltiple;
Sjögren;
Sarcoidosis;
Tratamiento;
Inmunosupresores

Esclerosis multiple y enfermedades reumatologicas: Behçet, sarcoidosis, Sjögren

Resumen
Introducción: La Esclerosis Multiple se puede asociar a varios procesos reumatológicos. La Enfermedad de Behcet (EB) es una vasculitis, inmunomediada crónica recurrente multisistémico de origen desconocido con solapamiento clínico con muchos procesos autoinflamatorios. La Sarcoidosis es una enfermedad granulomatosa multisistémica con distribución universal. El Sjögren (SS) es una enfermedad inflamatoria autoinmune crónica caracterizada por la presencia de infiltrados linfocíticos en las glándulas exocrinas lo que causa boca y ojos secos (xerostomía y

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xeroftalmía respectivamente). Dentro de las manifestaciones extraglandulares las más frecuentes son las músculo-esqueléticas.
Desarrollo: Las complicaciones neurológicas de estas enfermedades pueden ser múltiples. Se exponen las características más significativas de las mismas. También se describen los fármacos que pueden estar indicados en estos procesos así como la posibles contraindicaiones que pudieran existir con el tratamiento de la EM.
Conclusiones: Se exponen las principales recomendaciones para la el tratamiento de pacientes con EM que se asocien a estas enfermedades reumatológicas y en algunos casos obliga a evitar su uso en pacientes.
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Multiple sclerosis and neuro-Behçet disease

Behçet disease is a relapsing, multisystemic, immune-mediated chronic variable-vessel vasculitic disorder of unknown origin. An association with *HLA* class I genes is well established. From a clinical viewpoint, the condition overlaps with many autoinflammatory diseases. It is characterised by simultaneous or sequential development of mouth ulcers, genital ulcers, uveitis, skin lesions, pathergy reaction, arterial or venous thrombosis, arthritis, inflammatory bowel disease, and central nervous system (CNS) involvement.

From an epidemiological viewpoint, its incidence varies across geographic regions, with higher prevalence rates in Turkey and lower prevalence rates in the United Kingdom, Portugal, Spain, and the United States, ranging from 0.64 to 6.4 cases per 100,000 population. It affects men and women similarly and manifests in the third or fourth decades of life; more severe forms usually present in young adults over the age of 30.

Regarding the aetiopathogenesis of the condition, Behçet disease has an autoinflammatory and autoimmune basis, with involvement of the innate and adaptive immune systems, genetic factors (HLA-B51 in 50% of cases, and a weaker association with HLA-A26), autoantigens, and environmental antigens (such bacterial antigens as *Streptococcus* spp. and *Prevotella* spp., herpes simplex virus, or cytomegalovirus).

Neuro-Behçet disease (NBD) presents in fewer than 10% of cases, typically 5–6 years after the initial diagnosis of Behçet disease and is more frequent in men. It manifests with a wide range of neurological symptoms, depending on the location of the lesion, most of which are focal parenchymal lesions associated with vascular thrombosis (spinal cord, brainstem, cerebellum, basal ganglia, thalamus, internal capsule, periventricular white matter). However, the condition can also be associated with non-parenchymal lesions, including thrombotic stroke, acute meningeal syndrome, and dural sinus thrombosis. Intracerebral venous sinus thrombosis manifests with increased cerebrospinal fluid (CSF) pressure, papilloedema, and headache. Parenchymal lesions are more frequent in adults with NBD, whereas non-parenchymal lesions are more common in children. The most frequent symptoms are motor alterations, memory impairment, and personality disorders, as well as other symptoms that depend on lesion location. Symptoms are frequently subacute and correlate with MRI lesions.

Diagnosis is based on clinical, neuroimaging, and CSF findings. Early diagnosis is essential, as treatment depends on the organic lesion and its severity. MRI reveals lesions extending from the brainstem to the grey nuclei, or discontinuous lesions extending to the spinal cord; lesions may be uni- or bilateral, and measure 4–10 mm in diameter.[1] Acute and subacute lesions appear as T2-hyperintense foci, with greater signal intensity after contrast administration, whereas chronic lesions do not intensify after contrast administration and are associated with loss of brain volume. CSF analysis frequently detects a predominance of neutrophils, as well as increased levels of proteins and cells.

Given the variability of clinical manifestations of NBD, differential diagnosis includes a wide range of diseases. In most cases, the condition develops after several years with non-neurological manifestations; in these cases, diagnosis is relatively straightforward. However, when NBD appears in isolation or concurrently with Behçet disease, differential diagnosis must include other conditions, mainly multiple sclerosis (MS), thromboembolic stroke, meningoencephalitis, and reversible cerebral vasoconstriction syndrome.

NBD mimics many features of MS, including its higher frequency among young adults, relapsing–remitting or progressive course, presence of such cognitive disorders as memory impairment and frontal lobe dysfunction, presence of perivascular inflammatory cell infiltration on tissue biopsy, T2-hyperintense lesions, evoked potential alterations, and response to corticosteroid and immunosuppressant therapy.[1]

This overlap of symptoms and MRI findings hinders diagnosis in early stages of the disease and delays proper treatment. However, some findings help us to differentiate NBD from MS. For example, parenchymal involvement on MRI is typically seen in the basal ganglia and diencephalon in patients with NBD, and in the periventricular white matter in patients with MS, with lesion location potentially changing over time.[2] On the other hand, CSF is characterised by T-cell infiltration and oligoclonal bands in patients with MS, and predominantly neutrophilic infiltration and greater TNF-α expression in patients with NBD.

Accurate diagnosis is essential for treatment. Patients with Behçet disease and CNS involvement present a poorer prognosis; therefore, they are eligible for immunosuppressant/immunomodulatory treatment, in addition to corticosteroid therapy. No clinical trial has been conducted to determine the optimal management of NBD.[3] Induction treatment for severe forms of NBD is based on the administration of high doses of corticosteroids, with subsequent tapering over the course of 3–6 months.

The first-line immunosuppressant drug is azathioprine, dosed at 2.5 mg/kg/day, although anti-TNF therapy may be used as the first line of treatment in severe forms (encephalitis, medium vessel vasculitis, and parenchymal lesions).[4] Anti–TNF-α agents (infliximab [dosed at 5 mg/kg] and adalimumab [40 mg twice weekly]) are recommended in refractory cases or as second-line treatments, with observational studies showing favourable results for both agents. Cyclophosphamide (effective in preventing relapses) and the anti-IL6R agent tocilizumab (effective for refractory forms) are recommended as third-line treatments, although further research is needed. Interferon α, highly effective in cases of ocular involvement, may also play a role in the treatment of refractory NBD. Rituximab (RTX), approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of such diseases as MS, has also shown efficacy and safety in cases with ocular involvement, constituting a treatment alternative for refractory forms.

In contrast, such agents as ciclosporin should be avoided due to the risk of exacerbating the neurological symptoms of NBD.[5,6] Due to the associated risk of demyelinating CNS lesions and/or worsening of MS, the use of anti–TNF-α agents is contraindicated when the diagnosis of NBD is not confirmed.

Although there is no consensus on treatment duration, withdrawal of corticosteroid therapy with a switch to another treatment with a better safety profile is recommended, depending on tolerance and clinical response. In cases of poor prognosis, long-term use of immunosuppressant treatment is required. Predictors of poor prognosis include cumulative damage due to the lack of neuronal regeneration, parenchymal lesions, HLA-B51 positivity, motor dysfunction, and brainstem involvement.[7,8]

Multiple sclerosis and sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology characterised by the presence of non-caseating granulomas in the affected organs. From an epidemiological viewpoint, the condition has a universal distribution, primarily affecting young adults (< 40 years), with a slight female predominance. Its incidence varies greatly between geographical regions and ethnic groups, with rates of 5–19 cases per 100,000 person-years in white populations; rates are up to 3 times higher in black populations in the United States.

The complex pathogenesis of sarcoidosis involves both the innate immune system (toll-like and NOD-like receptors, dendritic cells, and macrophages) and the adaptive immune system (Th1 and Th17 cells, regulatory T cells, B cells), leading to an exaggerated inflammatory response that results in the formation of granulomas in the affected organ. CD4+ T cells play an essential role in the formation and maintenance of granulomas, with the cytokines IL-2, IFN-γ, and TNF-α also being involved. However, the antigenic stimulus that triggers the disease is yet to be identified. An association has been suggested with occupational and environmental factors (proven only in the case of beryllium exposure), infectious agents (mycobacteria, propionibacteria), and genetic factors (the disease's phenotypic variability is believed to be associated with its genetic variants). The disease has also been associated with HLA class I B8 and HLA class II, encoded by the HLA-DRB1 and HLA-DQB1 alleles.

From a clinical viewpoint, lung involvement is the most frequent manifestation, occurring in up to 90% of cases, followed by nervous system involvement (neurosarcoidosis), in 5%–34% of patients in clinical series and 14%–27% of cases in post mortem studies. In patients with neurosarcoidosis, CNS and cranial nerve involvement occurs earlier and peripheral nervous system (PNS) involvement occurs at later stages. Sarcoidosis may occasionally manifest in the form of neurosarcoidosis, with exclusive involvement of the brain or spinal cord and no systemic manifestations, in up to 20% of patients. Diagnostic criteria include typical clinical and anatomical pathology findings, and exclusion of alternative diagnoses.

Neurosarcoidosis is considered an MS mimic[9] and should therefore be included in the differential diagnosis of patients with hyperintense lesions on brain/spinal cord MRI in general, and MS in particular. MS is much more prevalent than neurosarcoidosis. However, in patients with sarcoidosis who develop neurological symptoms, a diagnosis of neurosarcoidosis is considered to be more likely. Both neurosarcoidosis and MS may present either a relapsing or a progressive course. Optic neuritis (ON), uveitis, transverse myelitis, ataxic paraparesis, and brainstem syndromes are common in both diseases. Furthermore, neurosarcoidosis and MS present overlapping MRI alterations, typically multifocal lesions in the periventricular white matter and spinal cord.

However, neurosarcoidosis presents distinctive features that are not observed in MS, such as multiple cranial neuropathy, myeloradiculopathy with spinal root involvement, aseptic meningitis, alterations in the hypothalamic–pituitary–adrenal axis (diabetes insipidus), and hydrocephalus. Neurosarcoidosis is difficult to distinguish from MS based on ocular manifestations. However, anterior uveitis is much more frequent in patients with sarcoidosis, whereas MS typically manifests with unilateral retrobulbar ON; bilateral acute ON is detected in up to 30% of patients with neurosarcoidosis and in fewer than 1% of patients with MS. Regarding neuroimaging findings, spinal MRI reveals meningeal and nerve root involvement in neurosarcoidosis, but not in MS.

When neurosarcoidosis and MS overlap, definitive diagnosis is not always possible without histopathological confirmation. Histopathological analysis is usually needed to confirm a diagnosis of neurosarcoidosis, but rarely in MS, except in very atypical cases. When neurosarcoidosis is suspected, it is essential to study systemic manifestations of sarcoidosis (skin, eye, and lung involvement). However, establishing a definitive diagnosis in patients with isolated

forms of neurosarcoidosis remains challenging due to the limitations of CNS biopsy techniques.

Correct diagnosis is essential for selecting the most appropriate treatment. An incorrect diagnosis could deprive a patient with neurosarcoidosis of appropriate treatment, and a patient with MS may be exposed to specific treatments for neurosarcoidosis, such as anti–TNF-α agents, which may exacerbate their condition.

The clinical and radiological characteristics of MS and neurosarcoidosis are sufficiently specific to enable differentiation between the 2 conditions in most cases. MRI is useful for distinguishing neurosarcoidosis from MS, although some findings are common to both conditions, such as periventricular white matter lesions, which may be misdiagnosed as a demyelinating disease, such as MS; however, the latter typically affects 4 locations (periventricular, juxtacortical, infratentorial, and spinal lesions). On the other hand, patients with neurosarcoidosis typically present multiple cranial nerve involvement and leptomeningeal and dural lesions.

CSF findings that may help in the differential diagnosis include IgG oligoclonal bands (more frequent in patients with MS, and rarely positive in neurosarcoidosis), lymphocytosis, and elevated protein levels (more frequent in neurosarcoidosis). Angiotensin-converting enzyme (ACE), present in patients with systemic sarcoidosis and in a small percentage of those with neurosarcoidosis, even without systemic involvement, lacks sufficient sensitivity and specificity for the diagnosis of sarcoidosis and is not useful for monitoring treatment response. Furthermore, increased CSF levels of ACE are not sufficiently sensitive or specific for diagnosing neurosarcoidosis. Given that ACE levels may increase in such processes as infections and malignancies, other markers have been proposed, including the CD4+/CD8+ cell ratio and sIL-2R level.[10]

Such radiological techniques as PET/CT have proven useful in differentiating neurosarcoidosis from malignant lesions, but their usefulness for differentiating it from other inflammatory CNS diseases is unclear.

Simultaneous development of MS and sarcoidosis is possible, though atypical from an epidemiological viewpoint.[11] The pathophysiological mechanisms underlying this co-occurrence are unknown and may be linked to differences in susceptibility to MS and sarcoidosis based on genetic or environmental factors, among others.

Patients with biopsy-confirmed systemic sarcoidosis who present neurological manifestations are frequently diagnosed with neurosarcoidosis. However, the possibility of a concurrent neurological disease, such as MS, should not be ruled out. When clinical findings are inconclusive, the absence of MRI lesions typical of neurosarcoidosis supports a diagnosis of MS. Therefore, patients with systemic sarcoidosis displaying clinical and radiological findings suggestive of MS should be diagnosed with both systemic sarcoidosis and MS, rather than neurosarcoidosis.

Regarding treatment, corticosteroids constitute the first line of treatment for acute forms of both neurosarcoidosis and MS, although in MS, they are administered exclusively during relapses and for short cycles, whereas in neurosarcoidosis, corticosteroid treatment is administered for long periods and combined with immunosuppressants to prevent relapses when tapering the corticosteroid dose.

As neurosarcoidosis is a rare disease, treatment is based on expert opinions and small retrospective studies. It frequently includes such immunosuppressants as azathioprine, mycophenolate, cyclophosphamide, ciclosporin, leflunomide, and methotrexate as second- or third-line drugs,[12] although with partial response; methotrexate is the corticosteroid-sparing agent of choice, according to clinical practice guidelines.[13] Anti–TNF-α agents (eg, infliximab) have shown effectiveness in refractory forms of neurosarcoidosis; the current tendency is to use these agents earlier in the disease course, given their proven efficacy and good safety profile as compared with other immunotherapies.[14] However, given the risk of demyelinating CNS lesions and/or worsening of MS associated with the use of anti–TNF-α agents, the drug is contraindicated when the diagnosis of NBD is uncertain.

The immunosuppressants azathioprine, cyclophosphamide, and methotrexate have been used in MS; however, they are not recommended for routine treatment due to their limited efficacy.[15] Disease-modifying therapies for MS include such subcutaneous drugs as interferon beta (IFN-β), glatiramer acetate, and ofatumumab; such intravenous drugs as natalizumab, ocrelizumab, and alemtuzumab; and such oral drugs as teriflunomide, dimethyl fumarate, fingolimod, ozanimod, ponesimod, and cladribine. Cladribine is reported to be beneficial in some cases of neurosarcoidosis. IFN-β, on the other hand, may exacerbate or even trigger sarcoidosis due to its proinflammatory effects, causing increased IL-6 production in CNS astrocytes, apoptotic effects in T cells, and activation of antigen-presenting dendritic cells. Likewise, alemtuzumab and natalizumab increase the risk of sarcoidosis in patients with MS and should therefore be avoided in case of diagnostic uncertainty.[16] No data are currently available on the effects of fingolimod.

RTX is an anti-CD20 monoclonal antibody approved by the FDA and the EMA for the treatment of aggressive forms of neurosarcoidosis, as well as other diseases, such as neuromyelitis optica and MS. Its action mechanism involves B cell depletion (anti-CD20), which reduces the local Th17 response and, consequently, inflammation. Ocrelizumab, which shares the same action mechanism as RTX, has shown significant effectiveness in relapsing MS, although no data are available on its effects in sarcoidosis.[17]

In summary, in cases with overlapping clinical manifestations preventing a definitive diagnosis, patients with a diagnosis of MS who subsequently develop systemic sarcoidosis, or patients with systemic sarcoidosis who present neurological symptoms and probable demyelinating lesions on MRI, treatment should target both diseases. The treatment of choice should be established according to comorbidities, disease severity, and shared decisions.

Multiple sclerosis and Sjögren syndrome

Sjögren syndrome is a chronic, autoimmune, inflammatory disease characterised by lymphocytic infiltration in exocrine glands, causing xerostomia (dry mouth) and xerophthalmia (dry eyes). It also presents with extraglandular manifestations affecting the musculoskeletal, renal, pulmonary, haematological, and nervous systems.[18]

No systemic therapy has been approved for the treatment of the glandular manifestations (dryness) of Sjögren syndrome, and treatment does not always improve dryness.

The most frequent extraglandular manifestations of the syndrome are musculoskeletal problems (arthritis, arthralgia, myositis [fibromyalgia]). These cases can be managed with non-steroidal anti-inflammatory drugs, low-dose corticosteroids, hydroxychloroquine, and/or methotrexate on a weekly basis. Patients with Sjögren syndrome may also present vascular involvement, with vasculitis and Raynaud phenomenon. Vasculitis may be treated with corticosteroids and/or cyclophosphamide (in case of polyarteritis nodosa). The neurological complications of Sjögren syndrome may involve both the CNS and the PNS. These neurological manifestations are diverse and may precede the typical glandular manifestations, delaying diagnosis.

CNS involvement includes diffuse abnormalities (psychiatric alterations, encephalopathy, aseptic meningitis, cognitive impairment/dementia) and focal or multifocal alterations of the brain and spinal cord that cause motor and sensory deficits, seizures, aphasia, and optic neuropathy.

A study has found that patients with Sjögren syndrome and CNS involvement present a higher prevalence of lung and kidney involvement, haematological alterations, positive results for antinuclear and anti-SSA antibodies, and C3 and C4 hypocomplementaemia than patients with Sjögren syndrome without CNS involvement.

Such severe neurological manifestations as mononeuritis multiplex and diffuse CNS involvement require high-dose glucocorticoids and immunosuppressants, such as cyclophosphamide and mycophenolate. Sensory polyneuropathy and ataxia usually respond poorly to high-dose glucocorticoids, whereas high-dose intravenous immunoglobulins may be useful in these cases. Neuropathic pain may be controlled with gabapentin, pregabalin, or venlafaxine, whereas tricyclic antidepressants should be avoided as they worsen dryness. RTX may be helpful in cases of severe CNS or PNS involvement refractory to conventional therapy with high-dose glucocorticoids and immunosuppressants; the drug seems to be more effective in controlling CNS symptoms than PNS symptoms.[19]

Treatment for lung and renal manifestations is based on the use of glucocorticoids, cyclophosphamide, and mycophenolate mofetil.

Aetiopathogenesis and prevalence

The aetiopathogenic mechanisms of Sjögren syndrome are yet to be fully understood. MS and Sjögren syndrome are associated with the same environmental factors: Epstein–Barr virus infection, cytomegalovirus infection, vitamin D deficiency, and smoking.

According to epidemiological studies, the prevalence of Sjögren syndrome in patients with MS ranges from 1% to 16.7% in patients with a primary progressive course. The incidence of sicca syndrome (presence of typical symptoms of Sjögren syndrome but not meeting diagnostic criteria for the condition) is up to 10%. In contrast, the prevalence rate of Sjögren syndrome in the general population is only 0.06%, indicating that Sjögren syndrome is more prevalent among patients with MS than in the general population. Furthermore, Sjögren syndrome affects the CNS in 5.8%–38% of cases, with CNS manifestations preceding a diagnosis of Sjögren syndrome in 52%–80% of these cases.

Treatments for Sjögren syndrome and multiple sclerosis

- Methotrexate. This drug is frequently indicated for rheumatic diseases, and particularly for the treatment of musculoskeletal alterations. It has been used as third-line treatment in MS and is also considered a disease-modulatory drug for MS, although with more limited efficacy than other options.

- Hydroxychloroquine. Primary progressive MS does not respond well to immunomodulatory or immunosuppressant therapies. Chronic microglial activation has been found to play a pathophysiological role.[20] Hydroxychloroquine reduces human microglial activity and has been found to present neuroprotective effects in vitro. Combination therapy with indapamide and hydroxychloroquine constitutes a novel treatment strategy for progressive MS. Evidence from animal studies suggests that hydroxychloroquine may decrease microglial activity and increase oligodendrocyte production by altering the expression of disease-associated miRNAs.[21,22]

- Cyclophosphamide. Cyclophosphamide continues to be a valid treatment option, especially in regions with limited access to high-efficacy therapies and in patients with highly relapsing activity and malignant course.[23] A recent study describes the case of a patient with concurrent MS and Sjögren syndrome who developed Hashimoto thyroiditis and primary biliary cirrhosis.[24] The patient was treated with cyclophosphamide, with good response. The literature also includes the report of a patient with Marburg acute MS (a severe form of MS) who improved with cyclophosphamide.[25]

- Rituximab. Over the past few decades, cumulative evidence has suggested that B cells play a direct or indirect role in the pathogenesis of MS. Particularly, RTX has been shown to reduce inflammatory activity, the incidence of relapses, and the development of new brain lesions on MRI in patients with relapsing–remitting MS.[26] Patients with progressive MS may also benefit from this treatment, as it presents good tolerability, acceptable safety, and a favourable cost-effectiveness profile. Although RTX has not been approved for the treatment of MS, and is therefore subject to different regulations for off-label use across countries, it is considered a valid treatment option for patients with MS in view of the increasing evidence on its efficacy and safety. RTX, a drug frequently used in rheumatic diseases, therefore constitutes one of the available anti-CD20 antibody treatments for MS management, together with ocrelizumab and ofatumumab.[27]

- Mycophenolate mofetil. Current evidence is insufficient to determine the efficacy of mycophenolate mofetil as an adjuvant to IFN-β 1a in patients with new-onset relapsing–remitting MS.[28,29] On the other hand, when used as an adjuvant therapy for the treatment of MS-associated uveitis, the drug was found to have beneficial effects on vision and intraocular inflammation, with an acceptable safety profile.[30] A subsequent study by Fakih et al.[28] found that mycophenolate mofetil did not alter disease progression, nor

did it reduce the relapse rate; other treatments should be considered before mycophenolate mofetil in cases of advanced progressive MS.[30]

Patient informed consent

No patient data are reported.

Ethical considerations

Not applicable.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2025.100198.

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